New FDA Commissioner to Face Vital Drug Safety Concerns: Companies Slow to Complete Postmarketing Trials

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In this case, the phase 4 trials provided critical safety information that was not available at the time of the approval. These studies allowed the FDA to consider returning natalizumab to the market, which the agency is likely to do while also requiring the companies to take additional precautions. These studies also should also help patients who are beginning a natalizumab regimen become aware of the potential adverse effects from PML, which had not been publicized before the phase 4 trials.

Yet many companies seem to drag their feet when it comes to completing phase 4 trials. That was the impression conveyed in the FDA's annual report, published in March; as of September 30, 2005, 65% of the 1,231 postmarketing studies pledged by companies were still pending.

John Jenkins, MD, Director of the FDA's Office of New Drugs, noted that 116 of the 797 studies had been promised during the 12 months ending in September 2005. Companies agreed to perform another 184 studies in the year preceding September 2004. Thus, most of the studies had been planned more than two years ago. Beyond that, however, Dr. Jenkins had a hard time simplifying the aggregated numbers in the confusing report.

One study, for example, was requested in the mid-1950s but had never been completed. Was it an important study? Is the drug still sold? For all we know, maybe it was a study of amphetamines used to treat Attention-Deficit/Hyperactivity Disorder (ADHD). Amphetamines have been used since the 1950s, and FDA advisory committees are now wondering whether ADHD drugs cause psychotic incidents and cardiovascular events.

In the recent past, phase 4 studies had usually been required for drugs indicated to treat life-threatening diseases, drugs that had been approved under the FDA's accelerated approval process. That was the case with Sanofi-Synthelabo’s oxaliplatin (Eloxatin), which was intended to treat metastatic colon or rectal carcinoma. The FDA approved oxaliplatin in January 2004 in just seven weeks (record time for a cancer drug). However, former FDA Commissioner Lester Crawford, DVM, noted that the drug had not extended the life of colon cancer patients and that it had a toxic effect on nerve endings that could cause either an acute or cumulative pattern of adverse effects. With that in mind, the FDA required Sanofi to complete one new phase 4 study and to send in paperwork on another study that had been completed. A Sanofi spokesperson could not specify whether the company has met those schedules.

The first thing Dr. von Eschenbach should do to prepare for the hearings is get his “number crunchers” to make the March postmarketing report more intelligible. Here are some questions to consider:

- How many of those pending studies are still necessary?
- How many studies are overdue by more than one year? By five years?
- Are there good reasons for these delays in each case?
- Does the FDA have a plan for hastening the completion of the important phase 4 studies?

In 2005, Senator Charles Grassley (R-Iowa), Chairman of the Senate Finance Committee, co-sponsored a bill with Senator Chris Dodd (D-Conn.). Their bipartisan bill would reorganize the FDA to bring about an improved focus on drug safety. For instance, it would give FDA the power to order unsafe drugs off the market immediately and to order drug companies to change drug warning labels. The bill—and the FDA’s record on phase 4 trials—will come up during the von Eschenbach confirmation hearings.

So Dr. von Eschenbach had better be ready with some good answers. And it wouldn’t hurt pharmaceutical companies to come up with a coherent presentation to explain phase 4 trial delays too.